all indefinite. An *acyl moiety* is *any* group of the structure RCO-. The metes and bounds of this term are perfectly clear to those of ordinary skill in the art. All of Applicant's prior arguments in this regard are reiterated here. Furthermore, Applicant has attached as Exhibit A, the results of a search of the US Patent and Trademark Office patent database, which shows that *more than 54,000* United States patents have been issued with the term "acyl" in their claims. Even a cursory review of these patents demonstrates that many contain no particular definition of the term; it is not necessary. Those of ordinary skill in the art understand what an acyl group is. The present claims provide a clear measure of what Applicant regards as the invention, and put the public on notice of the metes and bounds of the invention. The requirements of 35 USC § 112 are satisfied; the rejection should be removed.

"Heteroaliphatic, Aryl and Heteroaryl":

The Examiner has maintained his position that the terms "heteroaliphatic, "aryl" and "heteroaryl" are indefinite, but this time levies the accusation that the definitions presented in the specification "are not consistent with what is commonly known" (page 2 of the Advisory Action). Specifically, the Examiner states "there are no 3, 4, 5, 7, etc. aryl groups". That is incorrect. A tolyl group has seven carbon atoms and is aromatic; a seven-carbon aryl group therefore *does* exist. Moreover, the specification does not teach the reader of ordinary skill in this art that an aryl group could have only 3, 4, or 5 carbon atoms. The specification reads:

> "The terms 'aryl' and 'heteroaryl' as used herein refer to stable mono- or polycyclic-, heterocyclic, and polyheterocyclic unsaturated moieties having 3-14 carbon atoms which may be substituted or unsubstituted".

Those of ordinary skill in the art understand that some of the words in this definition refer only to "aryl" and others refer only to "heteroaryl", whereas others refer to either. For instance, no person of ordinary skill in the art would read this definition to mean that heterocyclic compounds are "aryl"; rather those of ordinary skill in the art would understand that heterocyclic compounds are "heteroaryl". Similarly, one of ordinary skill in the art would understand that 3-5 membered "aryl" rings do not exist; "heteroaryl" rings containing 3-5 carbons, however, do exist. Several such 3-5 carbon heteroaryl rings are specifically listed in the definition presented in the specification (e.g., 5-membered rings containing 3 carbons, such as: imidazolyl, pyrazolyl,

isothiazolyl, isoxazolyl, and thiazolyl groups; 5-membered rings containing 4 carbons, such as: pyrrolyl and furyl groups; 6-membered rings containing 4 carbons, such as: pyrazinyl, pyrimidinyl, and pyridazinyl groups; 6-membered rings containing 5 carbons, such as: pyridyl groups; etc.

The Examiner also states "a moiety having 3-14 carbon atoms can never be considered as a heteroaryl". In light of all of the examples of heteroaryl groups that fall within this definition, as well as the many others listed in the specification and still others apparent to those of ordinary skill in the art, this statement should be reconsidered and withdrawn.

The Examiner also states "the metes and bounds of heteroaliphatic is unknown". However, the Examiner has provided no indication of what is unclear. "Heteroaliphatic", as defined in the specification, means "aliphatic moieties that contain one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms". Those of ordinary skill in the art well understand the metes and bounds of an "aliphatic" moiety. As evidence of this, Applicant has attached as Exhibit B the results of a search of the US Patent and Trademark Office patent database, which shows that *more than 45,000* United States patents have been issued with the term "aliphatic" in their claims. A "heteroaliphatic" moiety, as recited in the present claims, is an aliphatic moiety including at least one heteroatom. There is nothing unclear in the term. The rejection for lack of clarity of this term should be removed.

Pharmaceutically acceptable ester, carbamate, metabolite or prodrug or salt

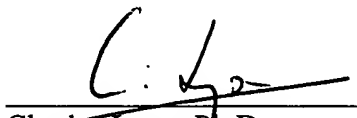
The Advisory Action states simply "the rejection over a pharmaceutically acceptable ester, carbamate, metabolite or prodrug or salt of such ester or carbamate remains". However, no such rejection previously existed. The prior rejection was of the term "pharmaceutically acceptable derivative". The Examiner has provided no evidence or argument that a person of ordinary skill in the art would have any trouble recognizing a pharmaceutically acceptable ester, carbamate, metabolite or pro-drug, or a salt thereof, of a claimed 28-epirapalog. The rejection, therefore, should be removed.

Conclusion

As required, attached hereto as **Appendix A** is a marked-up version of the changes made

to the claims by the present Amendment. For the reasons presented above, it is submitted that as amended the claims are allowable over the art of record. Please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,



Charles Lyon, Ph.D.
Agent for Applicant
Limited Recognition Under 37 CFR §10.9(b)

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April 28, 2003

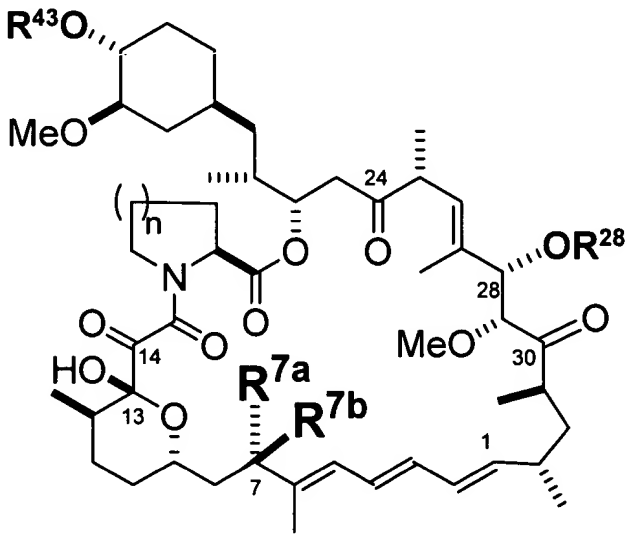
APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 20, 42 and 45 have been amended as follows:

1. **(Twice amended)** A compound of the formula:

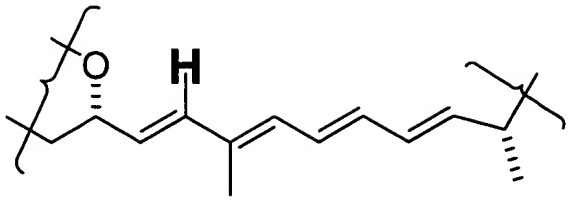


wherein

n is 1 or 2;

R^{28} and R^{43} are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

one of R^{7a} and R^{7b} is H and the other is halo, $-R^A$, $-OR^A$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO2R^A$, or $-NR^BSO2NR^AR^{B'}$; or R^{7a} and R^{7b} taken together, are H in the tetraene moiety:



where R^A is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety; ~~and~~

where R^B is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety;

where a heteroaliphatic moiety is an aliphatic moiety which contains one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms;

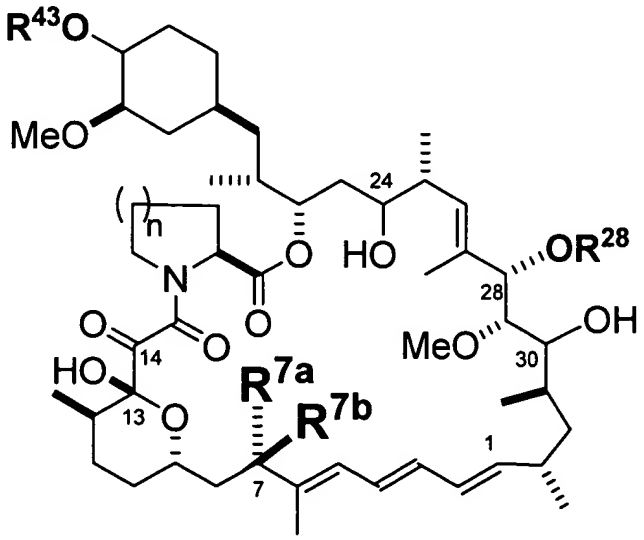
where an aryl moiety is a mono- or polycyclic unsaturated moiety having 3-14 carbon atoms; and

where a heteroaryl moiety is a mono- or polyheterocyclic unsaturated moiety having 3-14 carbon atoms;

or a pharmaceutically acceptable ~~derivative thereof~~ salt, ester, carbamate, metabolite or pro-drug thereof;

or a pharmaceutically acceptable salt of such ester or carbamate.

20. **(Twice amended)** A compound of the formula:

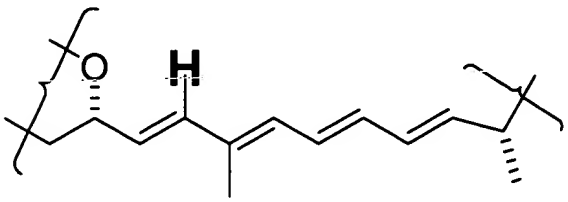


wherein

n is 1 or 2;

R^{28} and R^{43} are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

one of R^{7a} and R^{7b} is H and the other is halo, $-R^A$, $-OR^A$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO2R^A$, or $-NR^BSO2NR^AR^{B'}$; or R^{7a} and R^{7b} taken together, are H in the tetraene moiety:



where R^A is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety; ~~and~~

where R^B is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety;

where a heteroaliphatic moiety is an aliphatic moiety which contains one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms;

where an aryl moiety is a mono- or polycyclic unsaturated moiety having 3-14 carbon atoms; and

where a heteroaryl moiety is a mono- or polyheterocyclic unsaturated moiety having 3-14 carbon atoms;

or a pharmaceutically acceptable ~~derivative thereof~~ salt, ester, carbamate, metabolite or pro-drug thereof;

or a pharmaceutically acceptable salt of such ester or carbamate.

42. **(Once amended)** A method for ~~epimerizing the hydroxy group of an aldol moiety~~ producing a compound of claim 1 which comprises contacting a homologous C28 epimer ~~compound containing an aldol moiety~~ with a titanium tetraalkoxide reagent under suitable conditions and for a sufficient time to permit epimerization.

45. **(Once amended)** The method of any of claims 42-44 wherein the ~~aldol-containing~~ homologous C28 epimer ~~compound~~ is rapamycin ~~or a rapamycin derivative or analog~~.